UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BAYER SCHERING PHARMA AG and BAYER HEALTHCARE PHARMACEUTICALS INC., Plaintiffs, v. BARR LABORATORIES, INC., Defendant.	Honorable Peter G. Sheridan, U.S.D.J. Civil Action No. 05 CV 2308 (PGS)(ES) **Electronically Filed**

DEFENDANT BARR LABORATORIES, INC.'S TRIAL BRIEF

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I. PRELIMINARY STATEMENT

Bayer Schering obtained United States Patent No. 6,787,531 ("the '531 Patent") by concealing material information and submitting false and misleading declarations to the Patent Office, and thereby secured a monopoly on an oral contraceptive formulation containing the combination of micronized drospirenone and ethinyl estradiol. In this litigation, Plaintiffs assert this wrongfully-obtained monopoly in an attempt to block Barr from marketing a low-cost, generic combination oral contraceptive. However, Plaintiffs cannot succeed because the asserted claims of the '531 patent are plainly invalid as obvious and anticipated, as well as unenforceable due to inequitable conduct during the prosecution of the patent. [1]

Bayer Schering did not invent a combination oral contraceptive containing drospirenone and ethinyl estradiol, and it does not even claim to have done so. Rather, oral contraceptives containing drospirenone and ethinyl estradiol were known long before Bayer Schering filed its patent application. In fact, the results of long term studies using such an oral contraceptive were published nearly five years prior to Bayer Schering filing for its patent application. Bayer Schering's only alleged "innovation" was to use *micronized* drospirenone in the formulation to increase its bioavailability (the amount of drug absorbed by the body).

There is nothing novel about micronizing a poorly water soluble drug, which simply means reducing the particle size. Micronization has been known for decades as a way to increase the dissolution rate, and thus the bioavailability, of poorly water soluble drugs, like those often used in oral contraceptives. In fact, Plaintiffs' technical experts readily concede, as they must, that in formulating a combination oral contraceptive, it would have been obvious to micronize the poorly water soluble drospirenone and combine it with ethinyl estradiol.

[1] This Brief should not be construed as waiving Barr's right to litigate any issues that Plaintiffs, Bayer Schering Pharma AG and Bayer Health Care Pharmaceuticals Inc. (collectively "Plaintiffs" or "Bayer Schering"), may raise that are not specifically set forth herein.

Accordingly, Plaintiffs are not entitled to patent the idea of a dosage form containing micronized drospirenone.

Faced with this reality, Plaintiffs have shifted their theory and now argue that although one of skill in the art would have known to micronize drospirenone, he or she would have also immediately understood that because drospirenone might isomerize in acid, an additional step would be necessary: an enteric coating – i.e., a coating that protects the drug from being released in the stomach. But use of an enteric coating is not mentioned anywhere in the patent. To the contrary, the problem that the "invention" of the '531 Patent purports to solve is simply to increase the dissolution rate of drospirenone. The problem to be solved, as set forth in the specification, was *not* to protect the drospirenone from acidic conditions.

In any event, this last ditch argument cannot save Plaintiffs' patent because the Supreme Court recently held that when there are a finite number of predictable alternatives, an invention will be invalid as obvious if these alternatives would have been obvious to try. That is the case here. In formulating an oral contraceptive containing drospirenone, there were at most only two alternatives: simply using micronized drospirenone without an enteric coating, or using micronized drospirenone with an enteric coating. Given the finite number of alternatives available to solve the problem of a poorly water soluble drug, the use of one of those alternatives would have been obvious.

Not only would it have been obvious to try a formulation that contained micronized drospirenone without an enteric coat, this formulation, in fact, would have been the first choice of one of ordinary skill in the art. Enterically coating a micronized drug is not a panacea. Rather, enteric coatings are known to produce intra-subject therapeutic variability, have unpredictable results, and create manufacturing inefficiencies and expense.

In addition, Plaintiffs' patent is invalid for a completely different reason, prior public use under §102(b) of the Patent Code. 35 U.S.C. §102. A patent is invalid under the prior public use doctrine when the claimed invention was publicly used in the United States more than one year prior to the filing of the patent application. Plaintiffs publicly used the claimed invention in clinical trials conducted in the United States more than one year prior to filing its patent in 1999. Having previously assured that its product was effective through clinical trials in Europe, Plaintiffs conducted public clinical trials in the United States. The patients of the U.S. clinical trial were not subject to any confidentiality restrictions, nor were they under Plaintiffs' control. The patent law is clear that such an uncontrolled non-experimental public use precludes a later attempt to patent the product.

Finally, Plaintiffs' patent is unenforceable due to inequitable conduct before the patent office during the prosecution of the '531 patent. In an effort to overcome the patent examiner's repeated rejections of the claims on the basis that micronizing drospirenone would have been obvious, one of the named inventors submitted a false and misleading declaration that fundamentally mischaracterized the prior art at issue. In addition, Plaintiffs, in an attempt to overcome the invalidating effect of its public U.S. clinical trials, concealed material information about the trials and misrepresented their "experimental" nature to the examiner.

In sum, there is no basis in law for the '531 patent to exist, and it would never have been granted had Bayer Schering abided by its duty of candor to the PTO. Plaintiffs should not be permitted to monopolize the market for an oral contraceptive containing drospirenone and ethinyl estradiol for one more day under a wrongfully-obtained patent that Plaintiffs know to be invalid. The Court should find in favor of Barr.

II. BACKGROUND

Barr has challenged Plaintiffs' '531 patent pursuant to the Hatch-Waxman Act. Accordingly, Barr provides this brief background regarding the Act and the '531 patent.

A. Hatch–Waxman Act – ANDA Litigation

Under the Federal Food, Drug and Cosmetic Act, as amended by the Medicare Modernization Act of 2003, a company seeking approval to market a drug that has not previously been approved must file with the FDA a New Drug Application ("NDA"), which contains studies showing that the proposed drug product is safe and effective. 21 U.S.C. § 355(b)(1). The NDA must include, among other things, any patent that claims the drug or a method of using the drug. *Id.* The FDA publishes the patent information in connection with the NDA in its compendium of "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book." 21 U.S.C. §§ 355(b)(1), (j)(7)(A)(iii).

A company seeking approval of a generic version of an already approved NDA drug may file an Abbreviated New Drug Application ("ANDA") that relies on the safety and efficacy studies previously performed on the NDA drug. *Id.* § 355(j)(1)-(2). An ANDA applicant seeking to obtain approval prior to expiration of a listed patent must (with certain exceptions) submit a "Paragraph IV" certification, which states that the patent is invalid, unenforceable and/or will not be infringed by the proposed ANDA product. *Id.* § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

B. Plaintiffs' Product and The Patent-In-Suit

The commercial embodiment of the '531 patent is the oral contraceptive Yasmin®, which is a combination oral contraceptive containing both progestogen and estrogen components. The '531 patent is generally directed to a composition in an oral dose form containing 2-4 mg of micronized drospirenone and 0.01-0.05 mg of 17α-ethinylestradiol for use in a human female.

Plaintiffs sell Yasmin® tablets in the United States as a 28-day oral contraceptive regimen that consists of 21 tablets with each tablet containing 3 mg of drospirenone and 0.03 mg of 17α-ethinylestradiol, plus 7 placebo tablets.

The '531 patent issued on September 7, 2004, from U.S. Patent Application No. 09/654,227 ("the '227 application"), filed on August 31, 2000. The '227 application claims the benefit of U.S. Provisional application No. 60/240,953 ("the '953 provisional application"), filed on August 31, 1999. The primary question regarding the patentability of the claimed invention is whether it would have been obvious to one of ordinary skill in the art[2] to simply micronize a low dose drospirenone (a poorly water soluble drug in water), to increase its rate of dissolution and therefore overall bioavailability.

C. Barr's Abbreviated New Drug Application

Barr submitted its ANDA to the FDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of a generic version of Yasmin®. Pursuant to FDA regulations and 21 U.S.C. § 355(j)(2)(B)(iv), Barr sent a Notice Letter to Plaintiffs on March 18, 2005 advising them of its ANDA filing. Barr's Notice Letter explained in detail the basis for Barr's position that the '531 patent was invalid and/or would not be infringed by the manufacture, use, or sale of Barr's ANDA product. Shortly thereafter, Plaintiffs sued Barr, alleging that by filing its ANDA, Barr infringed the claims of the '531 patent.

[2] The concept of "one of ordinary skill in the art" will be used throughout this brief, as well as at trial. In general, this is a hypothetical person of ordinary skill in the art who is presumed to know all of the prior art to the '531 patent, as well as what the prior art "teaches" at the time the patent application was filed. The Supreme Court recently provided further clarification as to this hypothetical person: "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007).

D. Asserted Claims At Issue

Plaintiffs have asserted claims 1, 5, 8, 27-30, 33, 36, 49 and 50 of the '531 patent against Barr. Generally, each of the asserted claims requires that one of the active ingredients, drospirenone, be micronized. Each claim further requires that the formulation be effective as an oral contraceptive in human females and in an oral dose form exposed to the gastric environment upon dissolution. Claim 1 of the '531 patent is representative, and reads as follows:

> A pharmaceutical composition comprising: from about 2 mg to about 4 mg of micronized drospirenone particles, about 0.01 mg to about 0.05 mg of 17α-ethinyl estradiol, and one or more pharmaceutically acceptable carriers, the composition being in an oral dose form exposed to the gastric environment upon dissolution, and the composition being effective for oral contraception in a human female.

E. Scientific Background

The following is a brief summary of scientific concepts that may be discussed at trial:

1. Drug Absorption And Bioavailability

Drug absorption requires the drug molecules to be in solution at the site of absorption. The drug must be released from the dosage form (e.g., tablet) into the gastrointestinal fluids in order for the drug to be absorbed. This process is called dissolution.

In general, drug absorption from oral dosage forms occurs when a dissolved drug moves across the membranes of the gastrointestinal (GI) tract into the systemic circulation. The rate of this movement is directly related to the concentration of the drug at the absorption site (e.g. the stomach, the intestines, the colon or the rectum). The drug concentration at the absorption site is a function of the dissolution rate of the drug. Dissolution from the dosage form depends in part on the solubility of the drug in the GI fluids. Poorly water soluble drugs are often poorly absorbed, such that the amount of drug available in the systemic circulation is lower than desired. In such circumstances, the drug may have poor bioavailability because a sufficient amount of the drug does not get into the bloodstream. The dissolution rate also depends on the

surface area of the drug particles — especially in the case of poorly water soluble drugs. Therefore, increasing the surface area by reducing particle size (i.e.,. micronization) can markedly improve the rate of dissolution and therefore absorption. Accordingly, the bioavailability of a poorly water soluble drug will be improved by micronizing the drug.

2. Micronization

As indicated above, a key issue in this matter is the technique of including micronized particles of a poorly water soluble drug in a pharmaceutical compound. Micronization is, in general terms, the process of reducing the particle size of a substance, and, in particular, the process of reducing the average diameter of solid particles.

Micronization is a well known technique generally employed when formulating a pharmaceutical composition containing a poorly water soluble drug, such as drospirenone. There are essentially three reasons to micronize a poorly water soluble drug: (i) it increases the rate of dissolution (the compound dissolves faster); (ii) it increases the rate of absorption (the compound is absorbed into the body faster); and (iii) it improves bioavailability (more of the active ingredient actually makes it into the bloodstream).

There is a significant amount of publicly available scientific literature or "prior art" going back to at least as early as 1975 that discusses micronization of drugs. The micronization of sex steroids (including compounds virtually identical to drospirenone) is discussed in the prior art as early as 1982.

3. Isomerization

Isomerization is also an issue that Plaintiffs are expected to introduce in this case. Isomers are substances that are composed of the same atoms in the same proportions but have different arrangements of atoms in the substance. Plaintiffs will argue that the prior art suggests drospirenone may isomerize *in vitro* (i.e., outside the body) in certain acidic conditions.

Plaintiffs will further argue that this isomerization could impact the bioavailability of drospirenone, thereby impacting its efficacy. In particular, Plaintiffs will rely on a 1986 article published by Klaus Nickisch, a Bayer Schering employee (the "1986 Nickisch Reference") As a result of this reference, Plaintiffs will argue that one of ordinary skill in the art would not have considered it obvious to use micronized drospirenone in an oral contraceptive formulation. Barr flatly disagrees with Plaintiffs' interpretation of the 1986 Nickisch Reference and its applicability to the facts here.

In short, Plaintiffs rely almost entirely upon this single prior art reference that discusses an *in vitro* isomerization study conducted on drospirenone. This reference suggests drospirenone reaches an equilibrium (i.e., there is no change in the number of drospirenone molecules with its isomer) within three hours at room temperature when subjected to an acidic environment of pH 1.0. Plaintiffs argue that because of this piece of prior art, a person of ordinary skill in the art would not have expected success in using the micronized form of drospirenone in an oral contraceptive because micronization would ostensibly increase the rate of dissolution of the drug in the stomach, thereby causing more of the drospirenone to be isomerized. Plaintiffs argue that less active drug would get into the bloodstream if more drospirenone isomerized, which would thus decrease the bioavailability of the drug.

There are at least three prior art references authored by Krause et al. (Plaintiffs' employees) that would lead one of ordinary skill in the art to conclude that drospirenone does *not* isomerize *in vivo* (i.e., in the body). That is, unlike the 1986 Nickisch Reference, which simply reported on an *in vitro* study, these references reported that in *in vivo* studies, no isomer of spirorenone (whose chemical structure and *in vitro* isomerization profiles are nearly identical to drospirenone) could not be found in the plasma of patients administered a tablet containing

spirorenone. These studies concluded that the drug was absorbed before any drug was isomerized, if at all. The conclusions reached in these references would have confirmed to one of ordinary skill in the art that, while drospirenone might isomerize in certain static laboratory tests, it does not, in fact, isomerize in the human stomach. Thus, it would have been obvious to use micronized drospirenone in an oral contraceptive to increase its bioavailability.

4. Enteric Coating

An enteric coating is generally a pH-sensitive coating that prevents a drug from dissolving in the stomach. Barr anticipates Plaintiffs will argue at trial that drospirenone is an acid-sensitive drug and that there is scientific literature that teaches when there is a formulation containing an acid sensitive drug that may be exposed to acidic conditions (i.e., stomach juices), the formulation should be enteric coated.

The facts, however, will establish that the patent-in-suit does not mention anything about enteric coating. Moreover, between the mid-1980s and 1998, there was a significant amount of prior art published that discusses micronization of sex steroids, without any mention of enteric coating. During this time there was additional literature teaching that other acid sensitive drugs were not enterically coated, and by 1998, there were numerous commercially available combination oral contraceptives that were also not enterically coated. Thus, one of ordinary skill in the art in 1998, when faced with the applicable prior art *at the time*, would not have enterically coated a pharmaceutical composition containing drospirenone, as Plaintiffs suggest.

III. ARGUMENT

A. The Asserted Claims Are Obvious Under 35 U.S.C. § 103

The asserted claims of the ‘531 patent present a textbook case of obviousness and are invalid in view of the prior art. In particular, a person of ordinary skill in the art of formulating

drug products would have been motivated to formulate a combined oral contraceptive containing micronized drospirenone and 17α-ethinylestradiol.

1. Legal Standard Of Obviousness

35 U.S.C. § 103 provides, *inter alia*, that a patent may not be obtained if the differences between the subject matter sought to be patented and the prior art would have been obvious to a person having ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 3 (1966). The question of whether a claimed invention is unpatentable as obvious under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *McNeil-PPC, Inc. v. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003).

The Supreme Court in *KSR Int'l Co. v. Teleflex Inc.* recently significantly changed the landscape where obviousness is at issue, particularly in the context of patents whereby a company seeks to patent a combination of previously known elements. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). The Court flatly stated that "common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions" and that the "combination of familiar elements according to known methods is *likely to be obvious* when it does no more than yield predictable results." *Id.* at 1731 (emphasis added). The Supreme Court further concluded that a patent claim can be proved obvious merely by showing that the combination of elements was obvious to try:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. at 1741-42. This new standard rejected the rigid application of the prior teaching, suggestion and motivation ("TSM") test employed by the Federal Circuit in favor of a more flexible

obviousness standard. *Id.* at 1727. The Supreme Court also discussed the notion that certain improperly granted patents actually halt innovation: "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *Id.* at 1732.[3]

In *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007), the Federal Circuit applied the new standard of *KSR* and held that the inventors "merely used routine research methods to prove what was already believed to be the case." *Id.* at 1364. The Court noted that while the inventors may have advanced the state of the science, their experimentation merely proved conclusively what was strongly suspected before and nothing they did was inventive in nature. *Id*. Citing to *KSR*, the Court held that "[s]cientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *Id*. at 1363-64. (*citing KSR Int'l* 127 S.Ct. at 1732).

Similiarly, in *Novartis Pharm. Co. et al. v. Teva Pharma.,* this Court cited *KSR* for the proposition that "[i]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve a similar device in the same way, using the technique is obvious unless its actual application is beyond his or her skill." No. 05-CV-1887, 2007 U.S. Dist. LEXIS 65792, at *14 (D.N.J. Sept. 6, 2007) (citing *KSR* 127 S.Ct. at 1740). The Court accepted the generic manufacturer's argument that the modification to increase bioavailability of the product at issue was an "'ancient technology' that is exemplified in several

[3] The Federal Circuit has recognized that the principals set forth in *KSR* are applicable to pharmaceutical patents. *Takeda Chemical Indus., LTD v. Alphapharm Pty*, 492 F.3d 1350, 1353-54 (Fed. Cir. 2007). This Court has also affirmed the use of *KSR* in chemical compound cases. *See Novartis Pharm. Co. et al. v. Teva Pharma*., 2007 U.S. Dist. LEXIS 65792 at *14 (Sept. 6, 2007).

prior art references." *Id.* at *23. In fact, the patentee's expert admitted that the modification used is one strategy employed in the field. *Id*. Accordingly, the Court found that the patent in suit was obvious and stated that the "prior art teaching need not be that clearly articulated in terms of specific biologic data". *Id.* at *24.

2. The Asserted Claims Are Obvious In Light of the Prior Art

There are numerous pieces of prior art that conclusively demonstrate the obviousness of the '531 patent under the *KSR* standard.

Under the prior art, the only alleged new innovation is the micronization of drospirenone, nothing else. However, it was well known in the art at the time that: (i) the combination of drospirenone and ethinyl estradiol was used as an oral contraceptive; (ii) drospirenone was poorly soluble in water; and (iii) micronization was a commonly used technique to improve the rate of dissolution and bioavailability of a poorly water soluble drug. Based on prior art, it was obvious to one of ordinary skill in the art to micronize drospirenone in order to improve its rate of dissolution and increase its bioavailability. There is also no reasonable dispute that micronization had predictable results, namely, the particle size would be reduced, the dissolution rate would increase and more of the drug would be absorbed, thereby increasing its bioavailability. Plaintiffs have not pointed to one piece of prior art to suggest otherwise, because they cannot.

In fact, the only art Plaintiffs have been able to conjure up to argue otherwise is the 1986 Nickisch Reference, which provides virtually no useful information on bioavailability because it was an *in vitro* study that did not properly represent *in vivo* conditions. Plaintiffs apparently intend to argue that this reference suggests drospirenone may isomerize *in vitro* in certain acidic conditions. This isomerization, Plaintiffs posit, could potentially impact the bioavailability and efficacy of drospirenone. Thus, according to Plaintiffs, one of ordinary skill in the art: (i) would

not have considered it obvious to use micronized drospirenone in an oral contraceptive formulation; or (ii) would have considered it obvious to use micronized drospirenone in an oral contraceptive formulation but would have enteric coated the formulation to protect the drospirenone from the alleged isomerization.

The prior art, when viewed in its entirety (including the three Krause references, which reported that in *in vivo* studies, the isomer of a related compound was not detected), establishes just the opposite: there would have been no concern with micronizing drospirenone for use in a combination oral contraceptive without enterically coating the formulation.

Even if one of ordinary skill in the art would have been concerned with drospirenone isomerization *in vivo*, under the *KSR* standard there was a finite number of alternatives available to address the poor solubility of drospirenone, either enteric coat the formulation containing micronized drospirenone or do not. Plaintiffs cannot credibly argue that the use of one of those alternatives would not have been obvious.

B. There Are No Secondary Considerations That Can Save the‘531 Patent In Light of Barr’s Strong Showing of Obviousness

When a court reaches the conclusion that asserted claims are *prima facie* obvious, the patentee may attempt to present objective secondary considerations of nonobviousness. *WMS Gaming, Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999). The Supreme Court has recognized only three categories of secondary considerations—commercial success, long felt but unresolved needs, and failure of others. *Graham v. John Deere Co. of Kansas City*, 383 U.S.1, 17 (1996). “‘[A]rgument’ and ‘conjecture’ are insufficient in considering secondary considerations.” *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988) (citing *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984)). In fact, after *KSR*, courts have placed less emphasis on secondary considerations,

especially where there is a strong *prima facie* showing of obviousness, as there is in this case. The Federal Circuit post-*KSR* has held that secondary indicia of non-obviousness was not enough to save the day in light of an obvious invention. *Leapfrog Enter., Inc., v. Fisher-Price, Inc. & Mattel, Inc.* 485 F.3d 1157, 1162 (Fed. Cir. 2007) (holding held that even though the patentee "had provided substantial evidence of commercial success, praise, and long-felt need … the evidence on secondary considerations was inadequate to overcome a final conclusion that [the patented invention] would have been obvious."). *Id.*[4] Further, in attempting to rely on secondary evidence of nonobviousness, a patentee must establish a nexus between the evidence presented and the merits of the claimed invention, *i.e.*, the patentee bears the burden of demonstrating "a legally and factually sufficient connection" between the evidence and the patented invention to demonstrate that the evidence offered does, in fact, corroborate the invention's nonobviousness. *In re Paulson*, 30 F.3d 1475, 1482 (Fed. Cir. 1994); *see also In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Plaintiffs have indicated that they intend to rely upon the following secondary considerations: (i) unexpected results; (ii) commercial success; (iii) copying; (iv) skepticism; and (v) industry praise. The first two will be discussed below. Barr filed motions in limine relating to copying and skepticism, and Plaintiffs have not presented any support for their industry praise argument.

[4] Numerous courts post-*KSR* have expressed reluctance to allow secondary considerations to override a strong determination of obviousness. *See, e.g., Altana Pharma AG v. Teva Pharms. USA, Inc.*, No. 04-2355, 2007 WL 2688917, at *11 (D.N.J. Sept. 9, 2007); *Advanceme Inc. v. RapidPay, LLC*, No. 05-424, 2007 WL 2350644, at* 27 (E.D. Tex. Aug. 14, 2007); *Asyst Techs., Inc. v. Empak, Inc.*, No. 98-20451, 2007 WL 2255220, at *8-9 (N.D. Cal. Aug. 3, 2007); *Anderson Corp. v. Pella Corp.*, 500 F. Supp. 2d 1192, 1197 (D. Minn. 2007); *Friskit, Inc. v. RealNetworks, Inc.*, 499 F. Supp. 2d 1145, 1154 (N.D. Cal. 2007); *McNeil-PPC, Inc. v. Perrigo Co.*, No. 05-1231, 2007 WL 1933931, at *12-13 (S.D.N.Y. July 3, 2007).

1. Unexpected Results

"One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage *that a person of ordinary skill in the relevant art would have found surprising or unexpected*. The basic principle behind this rule is straightforward--that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (emphasis added).

The *KSR* Court recently clarified from whose perspective the obviousness inquiry is derived: "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. . . . The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. . . . " *KSR,* 127 S.Ct. at 1742. The results claimed by the patentee must be "unexpected" in comparison with what would have been expected by a person of ordinary skill in the art in light of the *closest prior art available*. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

Here, Plaintiffs will likely try to rely on certain internal studies from the early 1980's regarding enteric coating versus non-enteric coating to establish that it would not have been obvious to simply micronize drospirenone when formulating an oral contraceptive containing drospirenone without an enteric coating. That is, Plaintiffs will argue that one of ordinary skill in the art would have thought that when formulating the claimed invention, enterically coating the formulation containing micronized drospirenone would have been indicated. As support for this theory, Plaintiffs apparently will try to show that it was only after several years of testing enteric coated formulations that their own scientists decided to test non-enteric coated formulations, at which time they "discovered" that there actually was no need to enterically coat a formulation

containing micronized drospirenone because it did not isomerize in an *in vivo* environment. The results of these internal studies are legally irrelevant because what the inventor expected in the early 1980's has no bearing on the obviousness inquiry at the time the '531 patent application was filed in 1999.

Further, even if Plaintiffs can establish that these studies are somehow relevant, these studies fail to establish unexpected results. The analysis turns on what *one of ordinary skill in the art* would have expected at the time of the invention in 1999. Plaintiffs will likely try to establish that their "expectation" was that the only way to ensure efficacy and bioavailability of the product was to enterically coat it. Thus, Plaintiffs will argue, it was unexpected when they "discovered" that the product maintained its bioavailability and efficacy even though it was not enterically coated.

Plaintiffs, cannot rely on the internal data to purportedly establish an "expectation" that differs from the result they "unexpectedly" obtained, because that data on the expectations and results would be unknown to persons of ordinary skill in the art, and thus, the internal data cannot form the basis for that "expectation." Any purported expectation can only be derived from publicly available prior art. As set forth above, the prior art makes abundantly clear that the results of formulating micronized drospirenone in a non-enteric coated dosage form are exactly what one of ordinary skill in the art would expect: micronization improved dissolution and, therefore, overall bioavailability and efficacy. [5]

2. Commercial Success

A patentee offering evidence of "commercial success" to support a nonobviousness determination bears the burden of showing that there was, in fact, commercial success, and the

[5] *See In re Application of Jaeger*, 241 F.2d 723, 724-25 (C.C.P.A. 1957) (court held the alleged invention to be obvious, and noted that "[a] mistaken idea held by one or two workers in an art cannot be regarded as an accepted theory.")

requisite nexus that any such success is attributable to the claimed invention rather than to other, unrelated factors such as advertising or unclaimed features of the product. *In re Paulson*, 30 F.3d at 1482. Even a strong showing of commercial success, without more, may be insufficient by itself to counter strong evidence of obviousness. *See Newell Cos., v. Kenney Mfg. Co.*, 864 F.2d 757, 769 (Fed. Cir. 1988); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997). The weight that commercial success is given in an obviousness determination depends on both the extent of the commercial success, and the strength of the nexus between the commercial success and the merits of the claimed invention. *See Ashland Oil, Inc.*, 776 F.2d at 306 ("The objective evidence of secondary considerations may in any given case be entitled to more or less weight, depending on its nature and its relationship to the merits of the invention."). Any alleged inference of non-obviousness due to commercial success is weakened where the patentee's promotional campaign contributed to the alleged commercial success. *McNeil-PPC, Inc. v. Perrigo Co.*, No. 05-1321, 2007 WL 1933931 (S.D.N.Y. July 3, 2007).[6]

Here, the evidence will establish that any success Yasmin® realized was not as a direct and proximate result of the claimed invention, but from the substantial marketing and sales efforts employed by Plaintiffs. Yasmin®'s performance is almost entirely due to the selling, advertising and marketing efforts implemented and executed by Plaintiffs. There is not a scintilla of proof that the micronization or non-enteric coating of the product had anything to do

[6] In *McNeil*, the court noted that "[t]he evidence introduced at trial shows that McNeil spent over $90 million per year on advertising to promote the Pepcid brand. . . . Pepcid's overall brand strength weakens the inference that Pepcid Complete's commercial success arose from incorporation of the '340 invention. . . . Second, the advertising launch for Pepcid Complete was substantial; McNeil diverted more than one third of its total Pepcid brand advertising dollars to Pepcid Complete. . . . *The inference of non-obviousness arising from commercial success is weakened where the patentee's 'promotional campaign contributed to the patented [product's] commercial success.*'" *Id.* at *11-12 (quoting *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985)) (emphasis added).

with the sales of the product. In fact, if Plaintiffs had not committed the substantial resources and expenditures to actively market and promote the product, it would have been virtually impossible for the product to be recognized as a legitimate option in the area of oral contraceptives. Moreover, Plaintiffs have admitted that the purported benefits of Yasmin® (anti-bloating and acne control) have nothing to do with micronization. Further, one of Barr's expert witnesses will testify that physicians do not prescribe Yasmin® due to its micronization feature, and Plaintiffs have not challenged this opinion. For these reasons, Plaintiffs' commercial success arguments must fail.

C. The Asserted Claims Are Invalid Due To Public Use

The asserted claims of the '531 patent are invalid because Plaintiffs publicly used the claimed invention in the United States more than one year before the patent application was filed. Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless . . . the invention was in public use . . . more than one year prior to the date of the application for a patent in the United States . . . ." 35 U.S.C. § 102(b). This provision, known as the public use bar, "serves the policies of the patent system, for it encourages prompt filing of the patent applications after inventions have been completed and publicly used, and sets an outer limit to the term of exclusivity." *Allied Colloids, v. Am. Cyanamid Co.*, 64 F.3d 1570, 1574 (Fed. Cir. 1995). A public use includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor. *Netscape Comms. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002). Whether a patent is invalid due to a § 102(b) public use is a question of law based on the underlying facts. *Id.*

Here, the facts will show that the Plaintiffs' clinical trials in the United States involving the claimed invention were an invalidating public use prior to the critical date. Bayer Schering filed its patent application on August 31, 1999. Thus, the "critical date" for public use in this

case is August 31, 1998. Prior to this critical date, Plaintiffs conducted and completed a large public clinical trial in the United States in which the claimed dosage form was administered to human females. This clinical trial involved over 300 women who were repeatedly provided with Plaintiffs' claimed invention without any confidentiality obligations. Moreover, Plaintiffs did not maintain any reasonable control over the study, the participating women, or the drug samples provided to the women. For example, the women patients were given several months worth of the claimed drug product with no limitation or restrictions on what they could do with it. Indeed, some patients never returned to the study after receiving samples, and some of the unused product was never returned. As a result, the U.S. Clinical trials constitute a public use under 35 U.S.C. § 102(b).

Plaintiffs apparently will argue that the U.S. clinical trials were not a public use because they were experimental in nature. This argument is without merit. While the law recognizes that an inventor may test his invention in public without triggering the public use bar, this "experimental use" protection is not limitless. Rather it is well established that any protection from the public use bar afforded by experimental use necessarily ends when the invention at issue is "reduced to practice." *See e.g., New Railhead Mfg. Co. v. Vermeer Mfg. Co.,* 298 F.3d 1290, 1297-98 (Fed. Cir. 2002); *RCA Corp. v. Data Gen. Corp*., 887 F.2d 1056, 1061 (Fed. Cir. 1989); *Baxter, Int'l, Inc. v. COBE Labs., Inc.,* 88 F.3d 1054, 1060-61 (Fed. Cir. 1996). Any subsequent work with the claimed invention cannot be "experimental" as a matter of law. Therefore, a critical issue in this case is when plaintiffs reduced to practice the claimed invention and whether there was any public use of the invention thereafter and before the critical date of August 1998.

The evidence will establish that Plaintiffs' claimed invention was reduced to practice prior to the completion of the U.S. clinical trial, which occurred before the August 31, 1998 critical date. Thus, Plaintiffs' public use of the claimed invention prior to the critical date is not protected from the public use bar because the invention was already reduced to practice. Reduction to practice of a pharmaceutical composition occurs when the inventor "actually prepared the composition and knew that it would work." *Estee Lauder, Inc. v. L'Oreal S.A.*, 129 F.3d 588, 592 (Fed. Cir. 1997). Under 35 U.S.C. § 104(a)(1), reduction to practice of an invention can be established outside the U.S. in World Trade Organization member countries, which includes much of Europe. Moreover, reduction to practice from a patentability standpoint is in no way contingent on what the FDA requires of applicants. "Congress has . . . clearly expressed its intent to give statutory authority . . . to Federal agencies different than that given to the Patent Office. This is so because the standards established by statute for the advertisement, use, sale or distribution of drugs are quite different than the requirements under the Patent Act for the issuance of a patent." *In re Anthony*, 414 F.2d 1383, 1395 (C.C.P.A 1969) (quoting *In re Hartop*, 311 F.2d 249 (C.C.P.A. 1962)). Accordingly, "approval by the FDA 'is not a prerequisite' for the patenting of a new drug . . . [t]o put it another way, the FDA need not necessarily determine that a drug is commercially useful or usable before it may be 'useful' in the patent law sense."[7] *In re Anthony*, 414 F.2d at 1395.

[7] *See also Scott v. Finney*, 34 F.3d 1058, 1063-64 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness . . . is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings"); *see also Evans Medical Ltd. v. Am. Cyanamid Co. et al.*, 11 F. Supp. 2d 338, 367-68 (S.D.N.Y 1998) (finding an invention in public use despite FDA required testing, noting "There is no apparent reason why Takeda, after having established the efficacy and safety of its vaccine in Japan, would retest its vaccine in the United States, for any reason other than to obtain FDA approval for its sale and use here.").

Long before Plaintiffs initiated their public clinical trial in the United States, substantial work in formulating and testing the claimed invention occurred in Europe. In fact, the formulation of micronized drospirenone was first tested and developed by Plaintiffs in the early to mid-1980s. By January 1990, Plaintiffs had completed the claimed formulation of drospirenone and ethinyl estradiol drug product and had begun clinical testing throughout Europe. Dr. Renate Heithecker, one of the named inventors of the '531 patent, was in charge of Bayer Schering's European clinical testing for this product. The first Phase II clinical trials in humans in Europe took place in the early 1990s to determine the safety and efficacy of the formulation. On May 15, 1992, Dr. Heithecker authored a report that disclosed the results of one of the studies and concluded that the oral contraceptive tablet formulation comprising 3 mg drospirenone and 30 µg ethinylestradiol was safe and effective for human female use and was preferred over other potential formulations. Accordingly, Bayer Schering deemed this formulation its "final formulation."

Having determined the preferred formulation, Plaintiffs and Dr. Heithecker then immediately initiated a larger study, called a Phase III clinical study, in December 1992. This study was conducted on women throughout Europe using this "final formulation," and lasted until April 1996. During this Phase III trial, Dr. Heithecker and others within Bayer Schering and Bayer Healthcare Pharmaceuticals ("Bayer Healthcare") routinely met to discuss the status of the project. The meeting minutes of these conferences reveal that it was well understood by the core team members, including Dr. Heithecker, that the claimed invention worked for its intended purpose. For example, an August 16, 1995 document called a "Masterplan" concluded that the safety and efficacy of the claimed invention was "very good" and that "contraceptive reliability is well established." In addition, Dr. Heithecker authored the final report regarding the

European Phase III trial on April 20, 1998. In this report, Dr. Heithecker definitively concludes that that claimed invention was shown to be an effective, safe and well-tolerated, oral contraceptive.

Thus, the results of the European clinical trials conclusively demonstrate that the pharmaceutical composition described and allegedly claimed in the '531 patent was known to be safe and effective in human females, and therefore, reduced to practice as early as May 1992 (the date the Phase II trial were completed) and at the very latest by April 1998 (the date the Phase III Study Report was issued). Accordingly, at the very least, the administration of the claimed invention to human females in the U.S. clinical trial after April 20, 1998 constitutes public use and, as a result, renders the patent-in-suit invalid.

D. The '531 Patent Is Unenforceable Due To Plaintiffs' Inequitable Conduct

The '531 patent is also unenforceable due to Plaintiffs' intentional breach of the duty of candor, good faith and honesty in the patent application process, which constitutes "inequitable conduct." Plaintiffs' inequitable conduct stems from the applicants' submission of two materially false and misleading declarations to the patent office in obtaining the '531 patent and the related failure to inform the patent office of material information concerning the European clinical trials.

It is fundamental that all patent applicants have a duty to prosecute patent applications in the PTO with candor, good faith, and honesty. *Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co.,* 324 U.S. 806, 818 (1945). "The vital importance of this duty cannot be overstated. Without it, the edifice of patent law cannot stand. Indeed, the cornerstone presumption of an issued patent's validity, and the placement of a heavy burden on the infringer to show invalidity, both rest on the proper fulfillment of this duty." *Semiconductor Energy Lab. Co., Ltd. v. Samsung Elec. Co., Ltd.*, 4 F. Supp. 2d 477, 480 (E.D. Va. 1998.) A breach of this

duty of candor, good faith, and honesty constitutes inequitable conduct, and renders all claims of the patent involved unenforceable. *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1331 (Fed. Cir. 1998) (citing *Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1990)). Inequitable conduct includes "affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Molins PLC v. Textron, Inc.,* 48 F.3d 1172, 1178 (Fed. Cir. 1995).

In analyzing inequitable conduct, the court must discern whether the withheld references or misrepresentations satisfy a threshold level of materiality. *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1439 (Fed.Cir.1991). The court must also determine whether the applicant's conduct in this regard satisfies a threshold showing of intent to mislead. *Id.* "Intent need not, and rarely can, be proven by direct evidence." *Merck & Co. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989). Rather, intent to deceive is generally inferred from the facts and circumstances surrounding the applicant's overall conduct. *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005). While materiality and intent to deceive are two separate inquires, they "are often interrelated and intertwined." *Libbey-Owens-Ford Co. v. BOC Group, Inc.*, 655 F. Supp. 897, 916 (D.N.J. 1987). If the omission or misrepresentation is highly material to patentability, then less intent to deceive must be shown to elicit a finding of inequitable conduct. *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234 (Fed. Cir. 2003). Accordingly, "a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead." *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997).

The facts of this case will show that those owing a duty of candor to the patent office during the prosecution of the '531 patent violated their duty in two main ways: (1) by failing to disclose the results of the prior European clinical trials, which showed that the invention had been reduced to practice, and then mischaracterizing the U.S. clinical trial as "experimental", and (2) by mischaracterizing certain prior art references relating to micronization.

As explained in more detail above, there will be overwhelming evidence presented at trial that the European clinical trials established that the claimed invention was effective as an oral contraceptive in human females, and therefore the invention was reduced to practice prior to the conclusion of the public U.S. clinical trials and prior to the August 31, 1998 critical date. This reduction to practice removed any "experimental use" protection from public use bar. As such, the subsequent administration of the claimed invention during the U.S. clinical trials was a public use under 35 U.S.C. § 102(b).

Plaintiffs, however, never disclosed this material information to the Patent Office. Recognizing the public use problem created by their public U.S. clinical trials, in an effort to save their patent, the applicants submitted the declaration of Dr. Ellman. Dr. Ellman disclosed that the Plaintiffs had conducted a clinical trial in the U.S. prior to the critical date, but argued that these trials did not amount to public use under 35 U.S.C. § 102(b) because they were confidential and experimental. Dr. Ellman went so far as to say that U.S. clinical trials were "experimental in nature" because "Bayer Healthcare lacked the information needed to determine whether the Clinical Study Drug was safe and effective for its intended purpose." In light of the European clinical trials, this is simply false and misleading.

Had Dr. Ellman properly disclosed the results of the European clinical trials that had been completed much earlier, the examiner would have been on notice that the invention had been

reduced to practice, and thus, the U.S. clinical trials that took place prior the critical date were an invalidating public use. Similarly, had Dr. Ellman properly disclosed this information he could not have falsely represented as he did that the U.S. clinical trials were experimental in nature and therefore did not bar a grant of the patent under the public use bar of § 102(b). Accordingly, it is clear that the Dr. Ellman and the others substantively involved in the prosecution of the '531 patent intentionally breached their duty of candor.

The '531 patent is unenforceable for a second reason: The declaration of Dr. Lipp. By way of background, during the prosecution of the patent, on April 9, 2002, the Examiner rejected the then pending claims on the basis that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to employ drospirenone or ethinylestradiol in micronized form." In response, on March 10, 2003, the applicants filed a Supplemental Amendment and Reply, arguing that one of ordinary skill in the art would not have been motivated to use drospirenone in micronized form. In support of this argument, the applicants submitted the Declaration of one of the inventors, Dr. Ralph Lipp. In his Declaration, Dr. Lipp purports to explain why it would not have been obvious to one of ordinary skill in the art to employ micronized drospirenone. In so doing, however, Dr. Lipp materially mischaracterized the prior art upon which he relied. Thus, it is clear that Dr. Lipp intentionally breached his duty of candor to the patent office. Accordingly, the '531 patent should be declared unenforceable due to inequitable conduct.

IV. CONCLUSION

For the reasons set forth herein, as well as the reasons to be established at trial, the '531 patent should be declared invalid and unenforceable.

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